The relationship between Mycoplasma and Kawasaki disease in pediatric patients: An updated systematic review and meta-analysis

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ABSTRACT

Objectives: This study aimed to clarify the relationship between Mycoplasma pneumoniae (M. pneumoniae) and Kawasaki disease by conducting an updated systemic review and meta-analysis of published studies.

Materials and methods: Studies mentioning M. pneumoniae and Kawasaki disease before October 2022 were included in this meta-analysis. The pooled prevalence was calculated, and the log odds ratio in the random effects model was applied to estimate the pooled prevalence of M. pneumoniae infection in pediatric patients with Kawasaki disease. In addition, the clinical parameters, such as hemoglobin and erythrocyte sedimentation rate, were analyzed. Six studies with a total of 1,859 pediatric patients with Kawasaki disease were enrolled. The focused outcome was the pooled prevalence and clinical parameters.

Results: The pooled prevalence of M. pneumoniae infection was statistically significant in pediatric patients with Kawasaki disease. In addition, the values of hemoglobin and erythrocyte sedimentation rate were significantly different between M. pneumoniae-infected and non-M. pneumoniae-infected patients with Kawasaki disease. Other clinical parameters were not significantly different between M. pneumoniae-infected and non-M. pneumoniae-infected patients with Kawasaki disease.

Conclusion: The results suggest that M. pneumoniae infection is significantly prevalent in pediatric patients with Kawasaki disease. The lower values of hemoglobin and erythrocyte sedimentation rate in M. pneumoniae-infected patients with Kawasaki disease might be needed to investigate further.

Keywords: Erythrocyte sedimentation rate, hemoglobin, Kawasaki disease, meta-analysis, mycoplasma, pooled prevalence.

Kawasaki disease (KD) is a self-limited vasculitis with immune function alterations and contributes to the most cases of acquired heart disease in the children of developed countries and is an important cause of long-term cardiac disease in adulthood. The clinical features include erythema and cracking of lips, bilateral bulbar conjunctival injection without exudate, erythema of oral and pharyngeal mucosa, enlarged cervical lymph node, strawberry tongue, erythema and edema of the hands and feet in the acute phase, skin rash, and subacute periungual desquamation. The etiology of KD is still unknown and might be associated with some viruses. However, the relationship between the candidate viruses and KD have not been confirmed. In addition, the cell damage pattern and related oxidative stress molecules might be associated with the elevated

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proinflammatory cytokines and inflammasome, which might contribute to vasculitis and the inflammatory symptoms of KD. The postinfectious inflammatory response pathophysiology of KD might also be shared with the etiology for multisystem inflammatory syndrome for children.\(^6\)\(^7\) The laboratory parameters of several indicators have been mentioned in the differential diagnosis and clinical monitoring of KD,\(^8\) such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin, white blood cell (WBC), and neutrophil percentage.

*Mycoplasma pneumoniae* contributes to 10 to 40% of community-acquired pneumonia in children and is a common pathogen for respiratory tract infections.\(^9\) *M. pneumoniae* infection is a significant cause of hospitalization in the pediatric patients, particularly for children younger than six years old without typical clinical manifestations of pneumonia signs.\(^10\) In addition, *M. pneumoniae* infection is prone to have a longer course of illness within the community-acquired pneumonia.\(^11\) The coinfection of *M. pneumoniae* and other viruses might contribute to a more severe course of community-acquired pneumonia.\(^11\)\(^12\) Therefore, the *M. pneumoniae* infection should be well investigated in the pediatric population.

For the comorbidity of pediatric KD and *M. pneumoniae* infection, the previous studies found around 10 to 22% incidence of *M. pneumoniae* infection in pediatric KD patients.\(^13\)\(^-\)\(^15\) According to the literature above, pediatric KD patients are prone to heart disease, and *M. pneumoniae* infection contributes to most community-acquired pneumonia. The comorbidity of KD and *M. pneumoniae* infection might contribute to the more severe complications of the heart and lung in pediatric patients. The sequelae should be crucial for the clinical management of pediatric patients. In addition, there are still many unanswered questions of KD, particularly the comorbidity of *M. pneumoniae* infection and KD. Therefore, we conducted this systematic review and meta-analysis to confirm the relationship between pediatric KD and *M. pneumoniae* infection. In addition, the laboratory parameters were compared between a *M. pneumoniae*-infected group and a non-*M. pneumoniae* infection group of pediatric KD patients to establish any significant difference in the laboratory parameters.

**MATERIALS AND METHODS**

**Literature search and selection criteria**

The following keywords were used to search and collect the related articles in PubMed, Science Direct, EmBase, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL): “Mycoplasma,” “Kawasaki disease,” “infection,” “positive,” “negative,” “pediatric,” “children,” “hemoglobin,” “erythrocyte sedimentation rate,” “C-reactive protein,” “Mycoplasma pneumoniae,” or “outcome,” “comparison,” “versus,” “incidence,” “prevalence,” “white blood cell,” and “platelet.” The search was limited to the literature published or electronically published online before October 2022. The inclusion criteria for studies were as follows: (i) studies with data of *M. pneumoniae* infection and number of KD patients; (ii) comparisons between an *M. pneumoniae*-infected subgroup and a subgroup of patients with infections other than *M. pneumoniae* (the non-*M. pneumoniae* infection group) of KD patients; (iii) studies with detailed data of outcome in the perspective of infection, such as CRP, ESR, WBC, and neutrophil percentage; (iv) studies with detailed data on blood analyses, including hemoglobin, WBC, and platelets; (v) studies published in the journals of science citation index database in the English language. Consequently, six studies with a total of 1,859 pediatric patients with Kawasaki disease were included in the analyses.

**Quality assessment and data extraction**

We followed the Cochrane Handbook for Systematic Reviews and Interventions to conduct this meta-analysis. In addition, the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline was used for reporting our meta-analysis results.\(^16\) The following data were collected from the enrolled studies. First, the *M. pneumoniae* infection event and number of patients with KD. Second, the non-*M. pneumoniae* infection event and number of pediatric patients with KD. Third, the CRP, ESR, WBC, and neutrophil...
percentage of the *M. pneumoniae*-infected subgroup and the non-*M. pneumoniae* infection subgroup of pediatric KD patients. Fourth, the hemoglobin and platelet of the *M. pneumoniae*-infected subgroup and the non-*M. pneumoniae* infection subgroup of pediatric KD patients.

**Data extraction and critical appraisal**

Two reviewers assessed the abstracts, selected the articles, and then independently evaluated the full-text version of the selected studies. Afterward, the two reviewers independently extracted the focused data from the text, tables, and figures of the enrolled articles. The enrolled articles had data on the event and number of *M. pneumoniae* infections, detailed data on outcome in the perspective of infection (CRP, ESR, WBC, and neutrophil percentage), detailed data on outcome in the perspective of hematological parameters (hemoglobin, WBC, and platelet) in the full-text content. A collaborative review was conducted by all authors to achieve a strong agreement (kappa=0.8). All authors also reviewed the final results.

**Meta-analysis and statistical analysis**

The Cochrane Collaboration Review Manager (RevMan) software version 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2022) was used to perform the meta-analyses. For pooled prevalence of *M. pneumoniae* infection in KD, we generated pooled estimates of log odds ratios (ORs), along with the associated standard error (SE). Due to the lack of patient-level data, we used summary statistics for each study by extracting the reported ORs. In studies without ORs and SEs, we calculated these parameters according to the published data from each individual study for subsequently obtaining an estimate of ORs and SEs. The data was transformed to the log ORs using the ORs and SEs in the Rev Man calculation function. The risk estimates of individual studies were combined via the inverse variance-weighted averages of log ORs in the random-effects model. The risk estimates of individual studies were combined via the variance-weighted averages in the random-effects model. In addition, the random and fixed effects models were used with inverse variance function-weighted log ORs. The log OR results were used to determine if the prevalence of *M. pneumoniae* infection was significant in KD.

For continuous variables, the weighted mean difference was used to estimate numerical variables. The *M. pneumoniae*-infected and non-*M. pneumoniae* infection subgroups were compared to find if there was any significant difference for WBC, neutrophil percentage, CRP, ESR, platelet, and hemoglobin. The overall effect size of WBC, neutrophil percentage, CRP, ESR, platelet, and hemoglobin was calculated as the weighted average of the inverse variance for the study-specific estimates. The chi-square test was used to study heterogeneity between enrolled studies. The derived estimate of heterogeneity ($I^2$) was used to estimate statistical heterogeneity of studies included in the meta-analysis. Based on the Cochrane Handbook, the random effects model was used in the current meta-analysis. All $p$ values were two-sided. Publication bias was assessed using a funnel plot test. A $p$ value <0.05 was considered statistically significant.

**RESULTS**

**Enrollment of studies**

The PRISMA flow diagram of the current meta-analysis is demonstrated in Figure 1. The qualitative analysis of the remaining six articles was performed, and the remaining six studies were included in the quantitative analysis. The characteristics of the enrolled six studies are summarized in Table 1.

**Log OR of *M. pneumoniae*-infected versus non-*M. pneumoniae*-infected pediatric patients with KD**

The $I^2$ was 100%, which suggested a high heterogeneity in the sample of enrolled studies in this perspective. The test for overall effect was $Z=2.70$ ($p=0.007$), and the meta-analysis results showed a significant difference of log OR of *M. pneumoniae*-infected versus non-*M. pneumoniae*-infected pediatric patients with KD under random effects model. The results favored the *M. pneumoniae*-infected status in pediatric patients with KD (Figure 2).
The meta-analysis results for ESR in the comparison between *M. pneumoniae*-infected and non-*M. pneumoniae*-infected pediatric patients with KR.

The standardized mean difference between the *M. pneumoniae*-infected group and the non-*M. pneumoniae* infection group was 0.34 (95% CI: 0.07-0.62) in the random effects model, which suggested that the ESR of *M. pneumoniae*-infected group of pediatric KD patients was higher than that of the non-*M. pneumoniae* infection group of pediatric KD patients (test for overall effect Z=2.47, p=0.01). A significant heterogeneity was also noted [Tau²=0.03, Chi²=3.69, degree of freedom (df)=2 (p=0.16), I²=46%] (Figure 3).

The meta-analysis results for hemoglobin in the comparison between *M. pneumoniae*-infected and non-*M. pneumoniae*-infected pediatric patients with KD.

The standardized mean difference between the *M. pneumoniae*-infected group and the non-*M. pneumoniae* infection group was 0.45 (95% CI: 0.03-0.86) in the random effects model, which suggested that the hemoglobin of *M. pneumoniae*-infected group of pediatric KD patients was higher than that of the non-*M. pneumoniae* infection group of pediatric KD patients (test for overall effect Z=2.12, p=0.03). A significant heterogeneity was noted [Tau²=0.09, Chi²=6.11, df=2 (p=0.05), I²=67%] (Figure 4).
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Nonsignificant results

The standardized mean differences of WBC, neutrophil percentage, CRP, and platelet were not significantly different between the *M. pneumoniae*-infected group and the non-*M. pneumoniae* infection group in the random effects model.
DISCUSSION

In the current meta-analysis, we found that the M. pneumoniae–infected group was significantly different from the non-M. pneumoniae infection group in the log OR of event number in pediatric patients with KD. It suggested that M. pneumoniae infection might be significantly associated with pediatric KD compared to non-M. pneumoniae infections. Apart from the significant association of M. pneumoniae infection and pediatric KD, the infection and hematological parameters might be the potentially differentiating points between M. pneumoniae infection and non-M. pneumoniae infection in pediatric KD patients. Our meta-analytic results found that ESR and hemoglobin were significantly different between the M. pneumoniae-infected group and the non-M. pneumoniae infection group. It showed that M. pneumoniae infection might be associated with a significantly higher value of ESR compared to non-M. pneumoniae infections. In addition, M.
pneumoniae infection might have a significantly higher value of hemoglobin compared to non-M. pneumoniae infections. The results suggest that M. pneumoniae infection might be a distinct group of pediatric KD compared to non-M. pneumoniae infections. To our knowledge, this is the first meta-analysis study focused on a M. pneumoniae-infected subgroup of pediatric KD patients. The results of the current meta-analysis can provide valuable information for clinicians to focus more on pediatric KD patients with an M. pneumoniae infection. According to the obtained data, the cut-off values of abnormal ESR and hemoglobin levels might be undetermined due to the relatively low number of enrolled studies and variable range of ESR and hemoglobin of enrolled studies. Therefore, we recommend that pediatric clinicians examine complete blood count, CRP, and ESR in pediatric KD patients. If the elevated ESR and hemoglobin are noted without the abnormality of WBC, neutrophil percentage, CRP, and platelet count, pediatric clinicians should be vigilant about the possibility of a comorbid M. pneumoniae infection.

The incidence of M. pneumoniae infection in pediatric KD patients is around 10 to 22% in the enrolled studies. However, the comparison between M. pneumoniae infection and non-M. pneumoniae infections in the log OR of pooled prevalence has not been published in a previous study. In the current meta-analysis, the significant log OR of M. pneumoniae infection might represent that it might be significantly prevalent in pediatric KD patients. The comorbidity of KD and M. pneumoniae infection in pediatric patients should be cautioned in clinical practice, and clinical treatment due to the predisposing characteristics of immune function alterations in pediatric KD. The early treatment should be performed in pediatric KD comorbid with M. pneumoniae infection due to the concern of original immune function alterations of pediatric KD patients.

The alterations of hemoglobin and ESR have been reported in previous studies of M. pneumoniae infection. A study reported that severe M. pneumoniae infection might be associated with significant differences in hemoglobin and ESR. In addition, the study suggested that ESR might be an indicator among a combination of laboratory parameters to predict the severe form of M. pneumoniae infection. The M. pneumoniae infection of pediatric KD patients might lead to a more severe tendency due to the predisposing trait of immune function alterations in pediatric KD patients. Therefore, the hemoglobin and ESR might be important indicators to identify the M. pneumoniae infection in pediatric KD patients. A recent study also mentioned that hemoglobin values might be significantly different between M. pneumoniae infection and other groups of infection in pediatric patients. Another study of severe M. pneumoniae infection also suggested that ESR values could be decreased after the medication treatment. ESR has also been reported to be associated with the target protein expression of M. pneumoniae infection in pediatric patients. ESR values were also higher in pediatric patients with refractory M. pneumoniae infection, which suggested the predictive value of this biomarker for M. pneumoniae infection in pediatric patients. One of the enrolled studies also supported that the higher value of ESR might occur in M. pneumoniae-infected pediatric KD patients. Another enrolled study suggested that clinicians should alter their approach in pediatric KD patients with a higher value of ESR, which might be associated with M. pneumoniae infection. A previous study also supported the crucial role of ESR in the prediction of refractory subtype of M. pneumoniae infection. The elevation of ESR might be one of the clinical phenomenon of M. pneumoniae infection. The increase of ESR might suggest an increase in positively charged proteins and a decrease in negatively charged albumin in M. pneumoniae-infected pediatric KD patients. In the current meta-analysis, the M. pneumoniae-infected group did not have significantly higher values of CRP compared to the non-M. pneumoniae infection group of pediatric KD patients. It also corresponded to the previous study suggesting that ESR and CRP were different biomarkers and should be used in a context-dependent way. ESR has a longer half-life than CRP. Therefore, ESR might be useful for monitoring chronic inflammatory condition such as the M. pneumoniae infection of pediatric KD patients. The elevation of hemoglobin and ESR might represent a potential type of biomarker for pediatric KD
patients with *M. pneumoniae* infection under the impression of current meta-analysis results. However, a further, well-designed study in this perspective might be warranted to confirm this potential biomarker.

There were several limitations in the current meta-analysis. First, the enrolled studies were limited in sample size, and the total sample size in the current meta-analysis was still limited. Therefore, a large-scale study with a bigger sample size might be needed in the future. Second, the enrolled studies were retrospective or cross-sectional, not prospective or longitudinal. Therefore, a bias might not be avoidable under the current design of the meta-analysis and might alter the interpretations of our meta-analysis results. Future meta-analyses in this field can include prospective and longitudinal studies, which can decrease the bias and provide a more accurate viewpoint on *M. pneumoniae* infection in pediatric KD. Third, the low sample size of enrolled studies in several significant outcomes, such as ESR and hemoglobin, might limit the interpretations of the significant results. In addition, the moderate heterogeneity of significant results in the ESR and hemoglobin might be a concern issue. Fourth, the lack of patient-level data might also influence the interpretations of our results due to lack a full evaluation for patient-level covariates in across comparisons. It is impossible to confirm a possible subgroup effect related to patient age due to lack of patient-level data and limited number of enrolled studies. Fifth, a high heterogeneity was noted in the significant results of log OR of *M. pneumoniae*-infected versus non-*M. pneumoniae*-infected pediatric KD patients. This heterogeneity issue suggested that we should take the interpretation of our meta-analytic results with this issue as a consideration. Sixth, the definition and detection of *M. pneumoniae* infection are variable in the enrolled studies, which might influence the results. Finally, the lack of sex distribution and a variable age range in the months of age for pediatric KD patients in some enrolled studies might be another concern.

In conclusion, the results suggest that *M. pneumoniae* infection is significantly prevalent in pediatric patients with KD. The lower values of hemoglobin and ESR in *M. pneumoniae*-infected patients with KD might be needed to investigate further.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** Research idea and study design: ZG and CM; data acquisition: Z.G., C.M.; Data analysis/interpretation: Z.G., C.M.; Statistical analysis: G.L., Z.B.; Supervision or mentorship: Z.B.; All authors takes responsibility that this study has been reported honestly, accurately and transparently, and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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